OPTIMAL DESIGN OF EXPERIMENT FOR MEDICAL SENSORS CALIBRATION

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Abstract- This paper presents a framework for the optimal design of experiments for medical sensors calibration. A new software program, G-optimal, is developed to demonstrate the optimal design of experiment. This program has been used to find G-optimal design for amperometric enzyme glucose sensor, silicon capacitive absolute pressure sensors and electrochemical oxygen and carbon dioxide partial pressure sensors. The developed software improves the calibration accuracy, reduces the calibration cost, decreases the time and effort required performing a calibration and provides user friendliness.

Keywords Experiment design, Medical sensors, Calibration.

I. INTRODUCTION

Medical sensors are applied in almost each medical instrument to convert the physiological signals to electrical signals (current or voltage) which are appropriate for electronic processing. Highly accurate medical sensors are required particularly to assure the proper operation of the medical instrument upon which the doctor's decision is based. However, a practical medical sensor exhibits nonidealities caused by cross-sensitivity, nonlinearity, gain, offset, hysteresis and environmental effects [1], that affect the desired sensor response to the physiological quantity of interest. Thus, the output of the medical sensor cannot be interpreted as an accurate and reliable representation of the physiological quantity to be measured and certain measures must be taken to calibrate the sensor using reliable reference input signals (standard), such that its output can be accurately related to the physiological quantity.

Generally, the calibration methods of medical sensors can be grouped into analog methods and digital methods. The drawbacks of the analog calibration methods are circuit complexity, limited resolution, lack of flexibility and limited capabilities to handle the nonlinearity and cross-sensitivity problems [2], [3].

The digital calibration offers many possibilities for flexible, accurate and programmable calibration method [4]-[7]. The digital calibration method is usually implemented using a compensation formula for a desired medical sensor; the calculation of the coefficients in the compensation formula involves extensive computations usually carried out on a PC. With appropriate computerization, calibration can be performed quickly and efficiently. Thus, computerization can guarantee quality, accuracy, and repeatability.

To computerize the calibration process the mathematical functional form of the sensor compensation formula must be known. When such a formula of desired medical sensor is known, a calibration can be effected by making a set of measurements of the variables that appear in the compensation formula. For reasons of economy, one is interested in accuracy and efficiency of calibration. This demands consideration of the tradeoffs between accuracy and calibration cost, which is strongly related to the number of calibration points used in the determination of the coefficients in the compensation formula .

At present, different procedures are used to determine the number of calibration points and the settings of the variables used in the calibration [8], [9]. Once the functional form of the compensation formula is known, the following questions arise:

What is the best means of carrying out the required calibration?

What is the optimal number of calibration points in order to effect sufficiently accurate calibration?

At what values of the variables should these calibration points be taken?

What is the optimal calibration interval for medical sensors?

This paper draws upon the mathematical theory of optimal design of experiments to establish an appropriate framework for addressing questions and issues such as these.

II. OPTIMAL DESIGN OF EXPERIMENTS

The optimal design of experiment can be accomplished by using the optimization functions such as: E-optimality, G-optimality, D-optimality and I-optimality [10]-[12] or response surface method [13], [14]. In this paper the optimal design of experiment for medical sensor is accomplished using G-optimal or response surface

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method (RSM), depending on whether the sensor compensation formula is known or not known.

II. a. G-optimality

The G-optimal is a design that minimizes the worst-case expected error in prediction [10]. Such a design would minimize the worst case expected error in applying a given compensation formula, under the assumption that the functional form of the compensation formula is known. The mathematical model (compensation formula) of a medical sensor can be generally expressed by the following regression -model:

$$Y(x;B) = B_1 f_1(x) + B_2 f_2(x) + \dots + B_m f_m(x) \qquad (1)$$

and this allows for a broad class of functions, including multivariate polynomials such as $Y = B_1 + B_2x_1 + B_3x_2 + B_4x_1x_2$ or functions with non-linear terms such as $Y = B_1 + B_2 \ln x_1 + B_3 x_1 \ln x_2$. The functions of input variables $f_i(x)$ are assumed to be linearly independent.

In what follows, bold face denotes vectors and matrices, a superscript T denotes the matrix transpose operation, and a circumflex denotes expected value. A set of sensor output measurements represented by the column vector $\mathbf{V} = (Y_1, Y_2, \dots, Y_n)^T$ is made at a set of specified values of the independent input variables x with a set of random errors $\boldsymbol{\varepsilon} = (\varepsilon_1, \varepsilon_2, \dots, \varepsilon_n)^T$, the elements of which are assumed to have zero mean and constant variance σ^2,

$$\begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{bmatrix} = \begin{bmatrix} f_1(x_1) & f_2(x_1) & \dots & f_m(x_1) \\ f_1(x_2) & f_2(x_2) & \cdots & f_m(x_2) \\ \vdots & \vdots & & \vdots \\ f_1(x_n) & f_2(x_n) & \cdots & f_m(x_n) \end{bmatrix} \begin{bmatrix} B_1 \\ B_2 \\ \vdots \\ B_m \end{bmatrix} + \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{bmatrix} \qquad (2)$$

This can be written as $\mathbf{Y} = \mathbf{XB} + \boldsymbol{\varepsilon}$, where $\mathbf{X}$ is called the design matrix. From regression theory, the best unbiased linear estimator of the coefficients is given by $\hat{B} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{Y}$. Furthermore, the variances in the estimates of the parameters $\hat{B}$ are given by $\sigma^2(\hat{B}) = \sigma^2(\mathbf{X}^T\mathbf{X})^{-1}$, and the variance in the fit function is $\sigma^2(\hat{Y}(x)) = \sigma^2\mathbf{f}^T(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{f}$ where $\mathbf{f} = (f_1(x), f_2(x), \dots . f_m(x))^T$. Optimization of the worst-case expected variance of a regression model using G-optimality function will lead to a task of selection of design matrix $\mathbf{X}$, that satisfies the following condition:

$$\min_{X} \max_{x\varepsilon\Omega(x)} [\hat{y}(x)] \Rightarrow \min_{X} \max_{x\varepsilon\Omega(x)} \mathbf{f}^T(x)\,(\mathbf{X}^T\mathbf{X})^{-1} f(x) \qquad (3)$$

where $\Omega(x)$ is the space of independent variables at which the medical sensor will be used.

II. b. Surface Response Method

The G-optimal method requires the knowledge of the compensation formula of a calibrated medical sensor. If this formula is not known, then the surface response method (SRM) is a powerful tool for optimal design of calibration experiment. Moreover, the SRM is a useful method for determination the optimum operating conditions such as climate conditions for the sensors. The response of the medical sensors are usually affected by climate conditions. Using the surface response method, the optimum temperature, humidity, pressure, ..etc, that yield a maximum sensor's output can be determined. Determination of these optimal conditions is very important for practical applications of sensors in medical instruments. The surface response method is based on utilization of steepest ascent or steepest descent methods. The first step in the RSM is to find a suitable approximation for the true relationship between dependent and the independent variables. Usually, a low order approximation polynomial first order or second order in some region of the independent variables is employed. The response surface analysis is then done in terms of the fitted surface. For fitting second order response surfaces, a composite design was used.

III. HARDWARE IMPLEMENTATION

To realize the previous methods for optimal design of experiments, a computer-based system was developed. The " brain " of this system is the software which was written using object oriented programming language [15]. This developed software improves the calibration accuracy and provides user friendliness. Moreover, to simplify the acquisition of sensor response for different levels of the controllable factors set according to experiment design plan, an electronic system is built for this purpose (Fig.1). The output of A/D converter is connected to the parallel interface of personal computer (PC).

The basic operation of this system is as follows. First, the developed software evaluates the optimal number of calibration points, their values (experiment plan) and the calibration interval. These intervals are calculated using similar procedure to that suggested by [16].

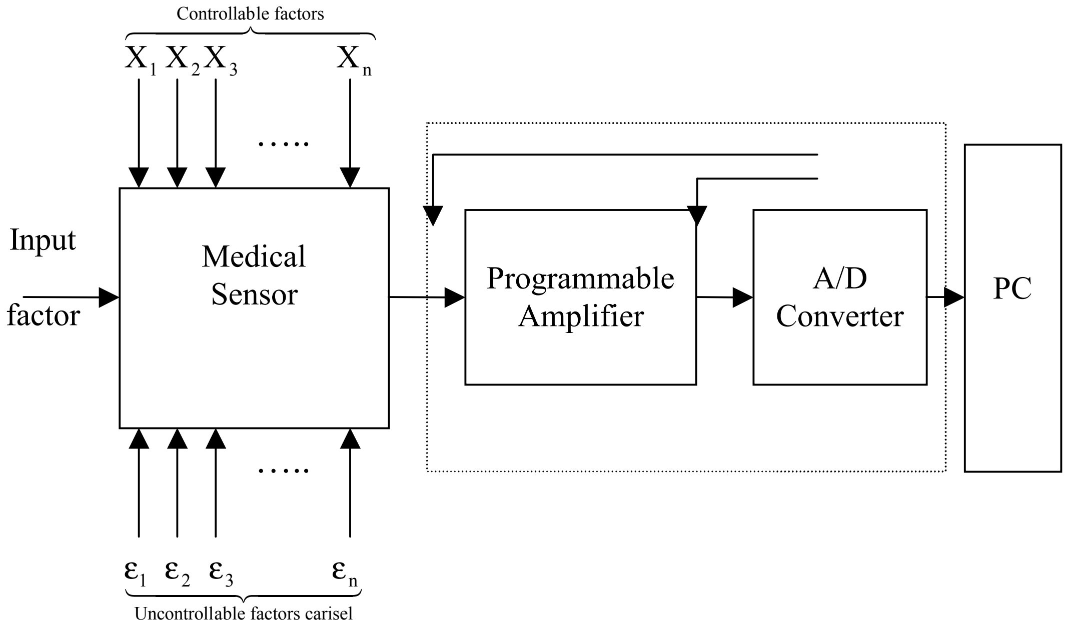

Fig. 1. Simplified block diagram of designed electronic system for automatic calibration of medical sensors

Of course, to determine the experiment plan, the developed software uses the G-optimal algorithm if the compensation formula is known or surface response method if this formula is not known. Then, the values of input and controllable factors are set according to the evaluated experiment design plan required for precise calibration of desired medical sensor. For each setting of these factors, the output of calibration sensor is amplified, digitized and then transmitted to PC through its parallel interface and stored in a special file in the PC. Next a new setting of input and controllable factors according to the evaluated experiment design plan is selected and the output signal of the medical sensor is again processed and stored in the PC. This procedure is repeated for all the different settings of input and controllable factors specified by evaluated experiment design plan. Then, the calibration factors that appear in the compensation formula for the desired medical sensor are determined using a special identification algorithm. This algorithm, which is based on regression methods, forms a main part of the developed software.

The designed digitally programmable bioelectric amplifier is shown in Fig.2. The transconductance operational amplifiers OTA1 and OTA2, [17], [18], forms digitally tunable (programmable) resistor. The value of this tunable resistor " Req " is given by:

$$R_{eq} = \frac{(2V_T)^2}{V_c} \frac{R_B}{|V^-| - 0.7} \tag{4}$$

Where V_T is thermal voltage (VT =26 mV for room temperature), V^- is the supply voltage and V_c is the control voltage. The value of V_c is controlled by the digital inputs that are set by the PC. Of course, the digital control of V_c causes a digitally regulation of Req. The differential voltage gain of the amplifier shown in Fig.2, is linearly proportional to R_{eq}, and thus, the realization of a digitally programmable amplifier is feasible.

If the resistors R_1, R_2, R_3 and R_4 are chosen to satisfy:

$$R_4/R_3 = R_1/R_2 \tag{5}$$

then the voltage gain (A_v) of the proposed amplifier is given by :

$$A_V = 1 + \frac{R_4}{R_3} + 2\frac{R_4}{R_{eq}} \tag{6}$$

Of course, the inputs of the amplifier (V1&V2) are connected directly to the output of calibrated medical sensor.

The main features of this amplifier are that it has a high common mode rejection ratio (CMRR=140 dB), low equivalent output noise voltage (V_n= 47.3nV), sufficient bandwidth for different medical applications (0 Hz – 200 Hz), high input resistance (Rin>100 MΩ) and low power consumption (less than 17mW). Moreover, the voltage gain of this amplifier can be easily adjusted and adapted for a wide range of medical applications, by digital programming of R_{eq}. The output signal of the designed amplifier is digitized using a 12-Bit A/D converter. The resolution of this A/D converter is 0.48 mV and its dynamic range is 72 dB. Moreover, it consists a three -state output buffer which makes it suitable for interfacing with the parallel interface of PC.

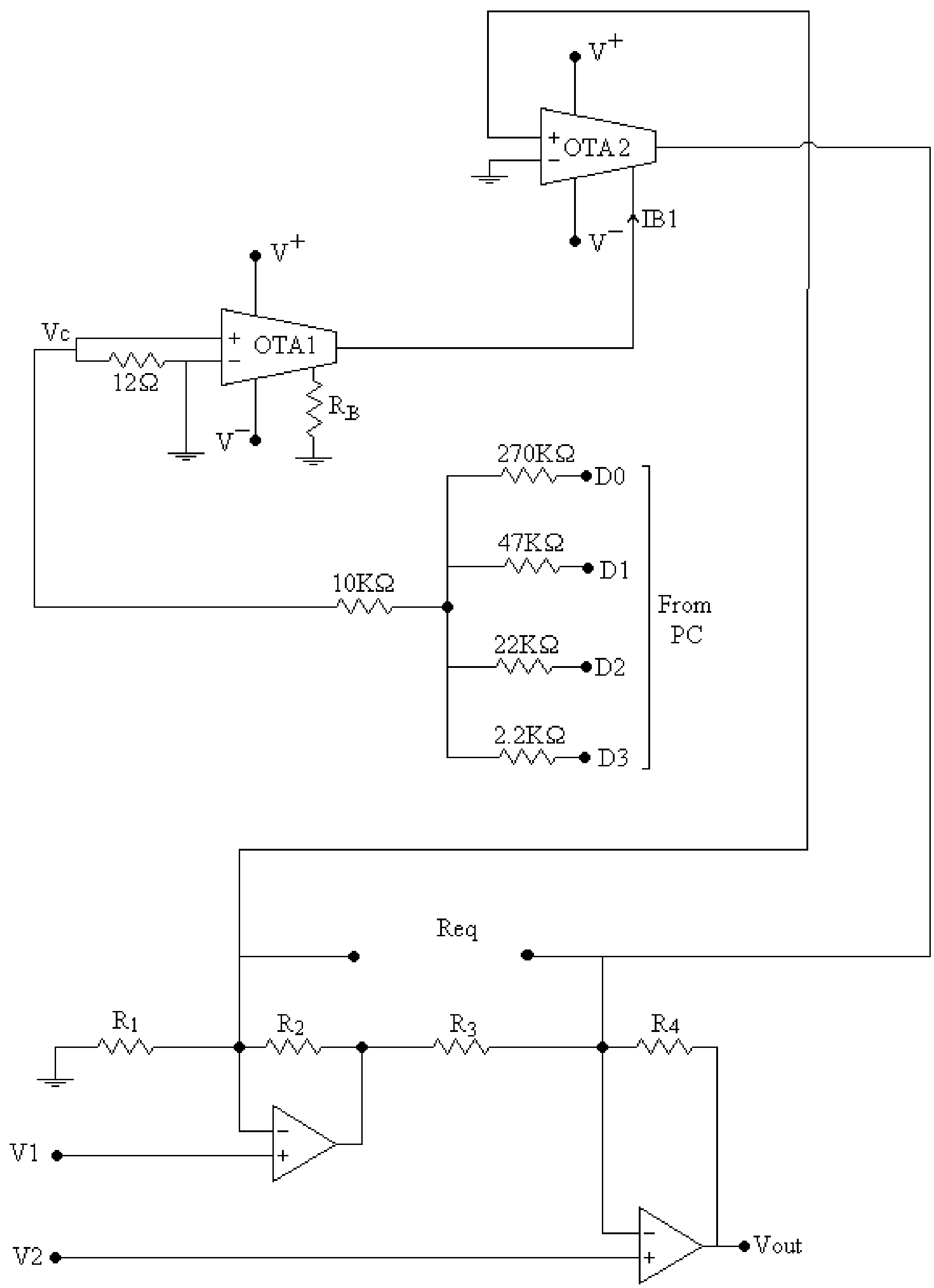

Fig.2. Circuit diagram of proposed digitally programmable amplifier .

IV. EXPERIMENTAL RESULTS

The previously discussed optimal design methods of experiments for medical sensors calibration were experimentally verified for different biosensors. Figure 3, shows the design found with G-optimality for a known a compensation formula of carbon dioxide partial pressure and a silicon capacitive absolute – pressure sensors.

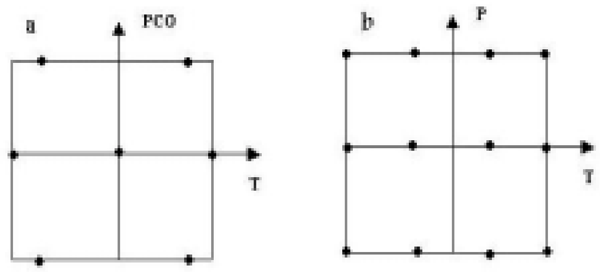

Fig.3 G-optimal design of calibration experiments for.
a) Seven terms carbon dioxide partial pressure (pCO_2) sensor.
b) Twelve-silicon capacitive pressure sensor.

Moreover, Table 1 shows a design found with a surface response method for an oxygen partial pressure sensor (its compensation formula is not known). The central composite design is used to fit the second-order response surface of investigated oxygen partial pressure sensor (Fig. 4) that have known compensation formula.

V. CONCLUSIONS

An optimal design of experiment for medical sensors calibration is presented. The design of experiment depends mainly upon whether the compensation formula of a sensor is known or not known. If it is known, then the G-optimal establishes one possible baseline for compensation of designs, and the G-optimal designs are particularly attractive to keep the number of experiments to a minimum. However if the compensation formula is not known, then the surface response method (SRM) should be used to design the experiment for sensor calibration.

The designed PC-based system for automatic calibration of medical sensors simplifies greatly the problems related with data acquisition, processing, and analysis. Moreover, the new developed software program, G-optimal, improves the calibration accuracy, reduces the calibration cost, decreases the time and effort required performing a calibration and provides user friendliness.

TABLE 1

Central composite design for oxygen partial pressure sensor.

Observation Number	Coded Variables				
	Temperature [degree]	PO_2 [mmHg]	T	PO_2	Current [uA]
1	20	60	-1	-1	31
2	40	60	1	-1	34
3	20	130	-1	1	43
4	40	130	1	1	48
5	15.86	95	-1.41	0	35
6	44.14	95	1.41	0	41
7	30	45.5	0	-1.41	28
8	30	144.5	0	1.41	45
9	30	95	0	0	37
10	30	95	0	0	38

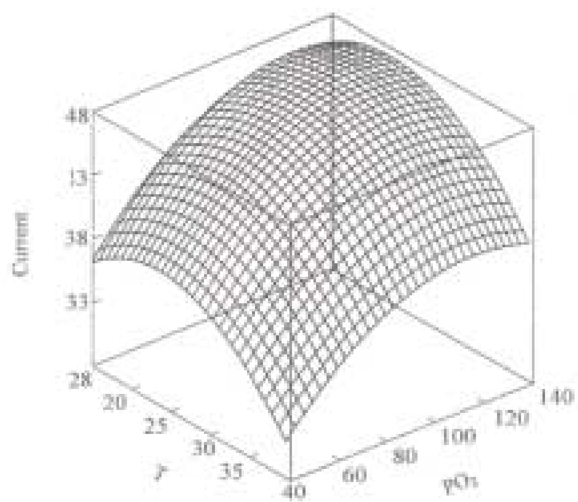

Fig. 4. Response surface plot for oxygen partial pressure sensor developed using the proposed automatic calibration system.

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